UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/380,200	01/30/95	BIRNSTIEL	M 0652.1080001

EXAMINER

18M1/1028

STERNE KESSLER GOLDSTEIN & FOX
SUITE 600
1100 NEW YORK AVENUE NW
WASHINGTON DC 20005-3934

EISENSCHENK, F

ART UNIT	PAPER NUMBER
1816	29

DATE MAILED: 10/28/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 8/12/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-40 is/are pending in the application.
Of the above, claim(s) 21-27,30,31,35 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-20,28,32-34,36-40 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ *are subject to restriction or election requirement.*

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ *All* ☐ *Some** ☐ *None* *of the CERTIFIED copies of the priority documents have been*

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Informal Patent Application, PTO-948

THE FOLLOWING PAGES--

15. This application contains claims directed to the following patentably distinct species of the claimed invention:

    1) wherein the nucleic acids are:
       A) HIV antisense oligonucleotides
       B) ribozymes

    These species are distinct because their biological mechanisms for the biological effects mediated by each specie is different. Ribozymes are enzymatically active molecules while antisense oligonucleotides are not enzymatically active molecules.

    Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 17-20 and 32 are generic with regards to Applicant's claimed protein-polycation-nucleic acid complexes.

16. During a telephone conversation with Robert Esmond on 8/17/93 a provisional election was made with traverse to prosecute the invention of species B, ribozymes, claims 28-29 and 33-34. Affirmation of this election must be made by applicant in responding to this Office action. Claims 21-27, 30-31, and 35 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. Claims 1-16, 36, 37, and 39 are eligible for examination under 35 USC 371 and have been examined accordingly. The Examiner has chosen to join a second "product" for prosecution in this Application wherein the product is a nucleic acid-protein polycation complex. To this end, a species election was required of Applicant and ribozyme type nucleic acids were elected. Claims reading on this specie are 17-20, 28-30, 32-34, 38 and 40.

17. Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

    Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

18. Generic claims 17-20 and 32 are present and are not allowable. In the above telephonic communication, Applicant was required under 35 USC § 121 to elect a single disclosed specie of nucleic acid should no generic claim be held to be allowable. Pursuant thereto, ribozymes were elected. Currently, claims 28-29, and 33-34 are readable on the elected invention species. Accordingly, claims 21-27, 30-31, and 35 are withdrawn from consideration under 37 CRF 1.142(b).

19. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

20. The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

21. Claims 1-20, 28-29, 32-34, and 36-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48-51 and 53 of copending application Serial No. 07/492460 in view of Wu et al., (AC1), Knapp et al., Goers et al. ('973). and Rossi et al. The claims in the copending application are drawn to transferrin-polynucleotide sequences which are useful for directing nucleic acids to cells expressing the transferrin receptor as are the claims in Wu et al. The claims in this application are drawn to protein-nucleic acid complexes where the nucleic acids are directed to cells by various targeting agents carrying

various forms of nucleic acids which are to be introduced into the cells as well as process claims for the introduction of the nucleic acid into the cells. The process claims are included in this rejection because the claimed process results, inherently, from the use of the targeting methods. Namely, the binding of the antibodies to the target antigen would result in the internalization of the complexes into the cells in a manner directly analogous to that observed in the transferrin targeting system. The variety of targeting systems disclosed by Applicant as useful for the targeting of nucleic acids to T-cells are obvious variants of the transferrin targeting system disclosed in the copending application or by Wu et al. Wu et al. teach that other targeting agents (i.e. hormones or antibodies) may be used to direct the conjugates to the target cell (see columns 5-6, The nature of the Ligand) and that targeting agent used will depend upon the target cell. The choice of antibody specificity for cell targeting, as disclosed by Goers et al. (see sections 5.1 and 5.3), is dependent upon the target upon which the artisan wishes to mediate a therapeutic effect. Knapp et al. teach a number of commercially available T-cell sepcific monoclonal antibodies. Applicant has also claimed the use of protein A-nucleic acid conjugates which bind to antibodies attached to a target antigen. This is an obvious variation of using the antibodies to target the nucleic acids directly since the protein A-nucleic acid conjugates would be binding to Fc portions of IgG molecules. Thus the targeting agent is still antibody dependent. Goers et al. further teach that the targeting agents disclosed in the patent also serve to direct target specific gene therapy and that the therapeutic agent used is dependent upon the biological effect desired by the intended therapeutic regimen, thus the use of T-cell specific antibodies to proteins which only bind to T-cells would be obvious targeting agents where T-cell therapy (targeting) is desired. Accordingly, the nucleic acid used in the therapeutic methodology is dependent upon the desired effect, i.e. antisense therapy or the introduction of ribozymes into the cells. Rossi et al. teach that ribozymes of any desired therapeutic effect may be targeted to cells using targeted liposomes. Such liposomes would be directed by antibodies to the desired cell (see column 6, Therapeutic Procedures). This is a provisional obvious-type double patenting rejection.

22. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views). Applicant is reminded to amend the specification to correspond to reflect any corrections made

to the drawings.

23. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

24. Claims 1-20, 28-29, 32-34, and 36-40 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. The specification fails to establish the utility of the claimed conjugates, complexes, and processes as having therapeutic efficacy in humans. Applicant's compositions have therapeutic usage as the intended utility for the invention and no support in the specification exists for this alleged utility. It is noted that Applicant is relying upon in vitro data to support the alleged utility and where the utility is drawn to human therapeutic utility, such evidence is not considered to be convincing.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

It is well known in the art that correlation between in vitro assays and in vivo animal studies to in vivo human efficacy is a major barrier. Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3). Applicant's compositions and processes do not utilize targeting agents which would be recognized as self by the human immune system. The invention appears to rely on the use of murine monoclonal antibodies and as is indicated in Harris et al., such antibodies lose effectiveness after their initial use because of the human anti-mouse antibody (HAMA) response. Applicant also proposes the use of gp120 as the targeting

agent for the conjugates of this invention. This protein, an admitted and art recognized antigen associated with the HIV virus would stimulate an immune response also resulting in its immunological inactivation in vivo. Anti-gp120 specific antibodies upon HIV infection are observed in HIV infected patients. Applicant also discloses that chloroquin is required to transfect cells in some instances. This is also an art recognized requirement of ensuring transfection (see Cotten et al. (AS1), page 4037, paragraph 2). Cotten et al. indicate that the cytotoxicity of chloroquin would limit the use of the transfection system in vivo. While the treatment of T-cells could be undertaken in vitro (ex vivo), the HIV virus is known to infect a large variety of cells and organs including neurons and the liver and is found in localized foci such as lymph nodes and the administration of chloroquin would have deleterious effects on the patient. Applicant has also failed to provide evidence within the specification that the ribozymes of the claimed targeted polycation complex are capable of mediating a therapeutic effect in vivo. Therefore it does not appear that the asserted utility of the claimed method for treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01 (p).

The provisions of 35 U.S.C. § 101 require that claimed subject matter must be useful to be eligible for patentability. Case law has established that utility may not be based on mere assertion, but rather must be definite and in currently available form. Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). Initially, the burden is always on the Examiner to establish some reason to doubt the asserted utility of the claimed invention. If the asserted utility is believable on its face to persons skilled in the art in view of the contemporary knowledge in the art at the time the application is filed, then the burden is on the Examiner to provide reasons or evidentiary proof to substantiate a rejection based on lack of utility under 35 U.S.C. § 101. In the instance wherein the statements would be deemed unlikely to be correct by one skilled in the art in view of the contemporary knowledge in the art, the burden of adequate proof shifts to the applicant. In order to provide proof of utility with regard to monoclonal antibodies (drugs) and their uses, either clinical, in vivo, or in vitro data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the art that the proposed utility is sufficiently established. See In re Irons, 340 F.2d 924, 144 USPQ 351 (CCPA 1965); Ex parte Krepelka, 231 USPQ 746 PTO Bd. Pat. App. & Inter. 1986); and Ex parte Chwang, 231 USPQ 751 (PTO Bd. Pat. App & Inter. 1986). When the utility is directed to humans, the data must

generally be clinical. In order to accept animal data, there must exist an art recognized animal model for testing purposes. See In re Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962).

25. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

26. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

A) Applicants have not disclosed how to use the claimed compositions, complexes, and processes therapeutically in humans. There is insufficient written description of the invention with respect to the in vivo operability of the invention as a therapeutic agent suitable for the treatment of humans for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see paragraph 24). Applicant also claims protein-A-polycation conjugates which would be useful for targeting nucleic acid into cells. This embodiment is not believed to be operable because no mechanism exists to prevent the administered protein-A-polycation-nucleic acid complex from bind serum IgG rather than target bound IgG in vivo. Upon administration to the patient, the protein-A will complex to IgG circulating in the vascular system and will, in all likelihood, be unable to reach the target site.

Therefore it does not appear that the asserted operability of the claimed method and compositions for inducing immune responses or treating HIV infection would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art.

27. Claims 1-20, 28-29, 32-34, and 36-40 are rejected under 35

U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see paragraph 26).

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. Claims 1, 6, 11, 13-18, 36, and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wagner et al. (AT2). Wagner et al. teach transferrin-polycation complexes which are capable of introducing nucleic acids into T-cells. The art recognizes that transferrin receptors are found on a variety of cells and that these receptors are identified as CD71 or OKT9 in the art (see the supplied CD guide). It is also known that transferrin receptor concentration is increased on metastic cells. Applicant's process claims for the introduction of nucleic acid into the cells are also taught by Wagner et al. in that the presentation of nucleic acid to cells would have resulted in the internalization of the nucleic acid in accordance with the claimed methodology.

30. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

31. Claims 2-5, 7-10, 12, 37 and 39-40 are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. and Knapp et al. Claims 2-5, 7-10, and 12 are drawn to protein-polycation conjugates wherein the targeting component of the conjugate is a T-cell specific monoclonal antibody or a protein that specifically binds to a T-cell antigen such as CD4 (i.e. the HIV protein gp120). The claims are also drawn to the use of modified histones in the in the conjugate and to protein-A-polycation complexes which would bind to antigen bound antibody molecules and using histones in the conjugates. Wu et al. teach a method of transfecting hepatocytes using asialoproteins conjugated to polycations for the transfection of liver cells (see abstract and column 4, paragraph 2). Wagner et al. teach the use of transferrin-polycation conjugates for the transfection of cells with DNA including the use of polylysine and protamine. Wu et al. teach a number of polycationic molecules useful in the instant invention, including histones, polylysine, etc (column 4, paragraph 2). Wu et al. teach that other targeting agents (i.e. hormones or antibodies) may be used to direct the conjugates to the target cell (see columns 5-6, The nature of the Ligand) and that agent used will depend upon the target cell. The references do not teach the use of T-cell specific antibodies for the targeting of polycation-nucleic acid complexes into cells. Goers et al. teach that therapeutic agents are selected for their intended application. Where the targeting of therapeutic agents to T-cells is contemplated, antibodies specific for T-cell antigens would be selected. Knapp et al. teach a variety of known T-cell specific antibodies which are commercially available. The substitution of such antibodies as targeting agents of protein-polycation complexes would have ben obvious to one of ordinary skill where the targeting of T-cell was desired. Such targeting would be desired when one wished to treat T-cell leukemias or HIV infected T-cells. The use of gp120 to target polycation-nucleic acid complexes to CD4 expressing cells would be functionally analogous to using anti-CD4 antibodies, and in view of the state of the art at the time of invention, an obvious means of targeting therapeutic agents to CD4 expressing cells. The use of protein-A-polycation conjugates to target DNA into cells is, likewise, an obvious variation on the targeting theme since the art recognizes that protein-A efficiently binds to the Fc portions of IgG molecules. Thus, protein-A could serve as an effective targeting agent of nucleic acid to antigen bound IgG molecules on the surfaces of cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to select T-cell specific

antibodies, protein-A or gp120 as the targeting agents for protein-polycation conjugates because such antibodies would allow for the specific direction and introduction of nucleic acid laden conjugates to T-cells for therapeutic purposes. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

32. Claims 28-29 and 32-34 are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. and Knapp et al. and Haseloff et al., or Rossi et al. ('019). Claims 28-29 and 33-34 are drawn to protein-polycation/nucleic acid complexes wherein the nucleic acid is a ribozyme and the targeting component of the conjugate is a T-cell specific monoclonal antibody or a protein that specifically binds to a T-cell antigen such as CD4 (i.e. the HIV protein gp120). Wu et al. teach a method of transfecting hepatocytes using asialoproteins conjugated to polycations for the transfection of liver cells (see abstract and column 4, paragraph 2). Wagner et al. teach the use of transferrin-polycation conjugates for the transfection of cells with DNA including the use of polylysine and protamine. Wu et al. teach a number of polycationic molecules useful in the instant invention, including histones, polylysine, etc (column 4, paragraph 2). Wu et al. teach that other targeting agents (i.e. hormones or antibodies) may be used to direct the conjugates to the target cell (see columns 5-6, The nature of the Ligand) and that agent used will depend upon the target cell. The references do not teach the use of T-cell specific antibodies for the targeting of polycation-nucleic acid complexes into cells or the use of ribozymes as a therapeutic agent. Goers et al. teach that therapeutic agents are selected for their intended application. Where the targeting of therapeutic agents to T-cells is contemplated, antibodies specific for T-cell antigens would be selected. Goers et al. also teach that therapeutic agents may be selected for their intended purpose and that such therapeutic agents include DNA or enzymes (see Section 5.3). Knapp et al. teach a variety of known T-cell specific antibodies which are commercially available. The substitution of such antibodies as targeting agents of protein-polycation complexes would have ben obvious to one of ordinary skill where the targeting of T-cell was desired. Such targeting would be desired when one wished to treat T-cell leukemias or HIV infected T-cells. The use of gp120 to target polycation-nucleic acid complexes to CD4 expressing

cells would be functionally analogous to using anti-CD4 antibodies, and in view of the state of the art at the time of invention, an obvious means of targeting therapeutic agents to CD4 expressing cells. Therapeutic agents of the gene therapy category also include ribozymes. Haseloff et al. teach ribozyme enzymes (ribozymes) and a variety of applications for these molecules (see pages 590-591) such as the specific targeting of a particular gene RNA transcript with ribozymes. The "anti-gene activity" of ribozymes is indicated to provide a basis for gene therapy of various diseases. This section also indicates that transfection or transformation techniques to introduce genes encoding ribozymes into various types of cells were known in the art in 1988. Those skilled in the art would have been able to insert ribozymes into a variety of genetic constructs in order to facilitate the expression of the ribozyme of a desired specificity. Rossi et al. teach ribozymes capable of cleaving HIV-1 RNA and provide a variety of therapeutic applications for the disclosed ribozymes of their invention. Included in this teaching is that therapeutic ribozymes may be introduced into cells by a variety of methods including the transfection of cells with DNA encoding the ribozymes of a desired specificity (see column 6, Therapeutic Procedures). Ribozymes are also taught to be capable of inactivating endogenous RNA transcripts including those produced by the ras, myc, or src oncogenes. In view of the teachings of Rossi et al. and/or Haseloff et al., one of ordinary skill would have recognized that ribozymes could have been targeted to cells using polycation-protein conjugates such as those taught by Wagner et al. Further, one of ordinary skill would have recognized, prior to Applicant's earliest priority date, that the targeting specificity of the system disclosed by Wagner et al. could be greatly enhanced by the use of antibodies to specifically target therapeutic agents such as ribozymes.

One of ordinary skill in the art at the time the invention was made would have been motivated to select T-cell specific antibodies, protein-A or gp120 as the targeting agents for protein-polycation conjugates because such antibodies would allow for the specific direction of ribozymes to T-cells for therapeutic purposes. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

33. No claim is allowed.

34. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Christopher Eisenschenk whose telephone number is (703) 308-0452. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

FE

F. Christopher Eisenschenk, Ph.D.
September 1, 1993

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
9/3/93